UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,165	03/09/2001	Harald Sobek	5328	4735

22829 7590 06/05/2002

ROCHE MOLECULAR SYSTEMS INC
PATENT LAW DEPARTMENT
1145 ATLANTIC AVENUE
ALAMEDA, CA 94501

EXAMINER	
SCHMIDT, MARY M	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/05/2002

10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/803,165	SOBEK ET AL.	
	Examiner	Art Unit	
	Mary Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 15-29 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 15-29 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Please note that the Examiner of record has changed in the instant Application. Applicant is requested to direct all future correspondence to Examiner Schmidt (see the concluding remarks below for information on how to reach the Examiner).

2. The response filed 3/14/02 has been entered. Claims 1-14 were canceled and claims 15-29 were added. The following rejections pertain to the new claims 15-29:

Claim Rejections - 35 USC § 112

3.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 is an incomplete process since the claim does not recite any method steps.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 26-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated host cells and methods *in vitro*, does not reasonably provide enablement for host cells in a whole organism or methods *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims

Claim 26 is drawn to a host cell comprising the DNA of claim 24 or the vector of claim 25. The host cell of claim 26 reads on a cell in a whole organism, and thus reads on a transgenic organism. The process of claim 27 also reads on purification of the mutant polymerase from a host cell *in vivo*. The specification as filed provides no guidance for expression of the claimed mutant polymerases in host cells in a whole organism.

The is a high level of unpredictability in the art for administration of nucleic acid constructs to cells in a whole organism for expression of recombinant proteins. Such methods encompass gene therapy via administration of the foreign protein via a vector to a whole organism for foreign expression of the protein. Anderson taught the pitfalls of administration of gene-therapeutic vectors to cells in a whole organism as "obtaining efficient delivery, transducing non-dividing cells, sustaining long-term gene expression." Other factors considered unpredictable include toxicity. Since neither the specification nor the art provided guidance for delivery of any mutant polymerase claimed to any host cell in a whole organism, one of skill in the art would have necessarily practiced "trial and error" experimentation to make and use the claimed invention for the scope of use in whole organisms. The amount of experimentation to

make and use the claimed invention in cells in a whole organism is considered undue in the absence of any clear guidance in either the specification or the art for expression of mutant *Thermococcus* polymerases in any whole organism, such as a human.

Claim Rejections - 35 USC § 103

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Claims 15-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Geneseq AAW29323 (the sequence in Frey et al., DE 196 11 759 A1) in view of Pisani et al. (Biochemistry) and Truniger et al. (J of Mol. Biol. and the EMBO J.) cited in the previous Official Action.

Claim 1 is drawn to a mutant polymerase comprising a Y-DD/A amino acid motif between an N-terminal 3'-5' exonuclease domain and a C-terminal polymerase domain wherein the tyrosine of the Y-GG/A amino acid motif is substituted with another amino acid, and wherein the wild-type form of the mutant polymerase has at least 80% amino acid homology to SEQ ID NO:34.

Geneseq AAW29323 teaches an amino acid sequence having 99.1% identity to instant SEQ ID NO:34 which is a DNA polymerase with 3'-5' exonuclease activity from *Thermococcus sp.* It does not specifically teach the Y-GG/A motif substitutions instantly claimed.

Pisani et al. and Truniger et al. are relied upon as set forth in the previous Official Action to teach the following:

Truniger et al. taught in the J. Of Mol. Biol. reference that "[t]he motif "YxGG/A", located in the connecting region between the N and C-terminal domains, and highly conserved in most DNA polymerases belonging to the eukaryotic-type superfamily, has been proposed to play a role in the coordination between synthesis and degradation.... Mutations in the YxGG/A region of ϕ29 DNA polymerase... affected the polymerase/exonuclease (pol/exo) balance of the enzyme, favoring either polymerization or exonucleolysis. These different phenotypes could be obtained by mutating a single amino acid residue and could be related to defects in stabilization of the Dna at a particular active site." (Pages 57-58) They further taught on page 59 that "[e]leven purified ϕ29 DNA polymerase mutant derivatives of the YxGG/A motif have been characterized here. The results obtained show that the YxGG/A motif is important for the correct and stable interaction of ϕ29 DNA polymerase and TP, controlling the pol/exo balance immediately after the TP-primed initiation step." They taught on page 60 the substitution of the tyr with a phe or ser (Figure 2) and on page 59 that "[t]he Tyr residue in motif YxGG/A is highly conserved in all eukaryotic-type DNA polymerases, being different only in three out of 33 cellular, bacterial and viral DNA polymerases." Therefore, while they did not specifically teach mutation of a polymerase from *Thermococcus aggregans*, they did teach the facts above that polymerases with YxGG/A motifs are common and that mutation of them lends to characterization of the most basic properties of the polymerase. They further taught in the EMBO reference that such

mutations give rise to different mutant phenotypes, including favored polymerization (abstract) and the location of the conserved YxGG/A motif in many polymerases from bacterial/viral, cellular and protein-priming polymerases (Fig. 1B, page 3432).

Pisani et al. further taught the mutation of the Y-GG/A motif in *Sulfolobus solfataricus* as cited in the previous Official Action. They did not specifically teach mutation of a polymerase from *Thermococcus aggregans*.

It would have been *prima facie* obvious at the time the invention was made to make a mutant polymerase having mutations of the Y-GG/A motif to form a mutant polymerase having at least 80% amino acid homology to SEQ ID NO:34 since (1) Pisani et al. and Truniger et al. both taught the motivation for mutation of the Y-GG/A motif in any polymerase having such a motif, including the substitution of the Tyr for a Phe or Ser (instant claims 20-23), for improved polymeration of the polymerases and (2) since SEQ ID NO:34 is 99.1% identical to the DNA polymerase having 3'-5' exonuclease activity taught by Geneseq AAW29323 which states that "the enzyme can specifically amplify nucleic acid fragments of up to 5 kB in high yields...." and which when harboring a Y-GG/A motif would have produced a mutant polymerase instantly claimed. It would have been further obvious to make a vector comprising said mutant and practicing methods of purifying said mutant and synthesizing nucleic acids from said mutant since DE 196 11 759 taught the expression of the pol. having 99.1% homology to instant SEQ ID NO:34 from a vector and all of the references cited taught use of the polymerases for amplification of polynucleotides.

One of ordinary skill in the art would have been motivated to substitute the Y-GG/A motif of a polymerase having said motif, such as the polymerase taught by Geneseq AAW29323, with different amino acids for the benefits taught by Truniger et al., improved polymerization. One of skill in the art would have been motivated to make vectors for expression of said mutants for the same reasons DE 196 11 759 taught making vectors for expression of the polymerase therein. Furthermore, one of ordinary skill in the art would have been motivated to use the mutant polymerase for amplification of nucleic acids since that is the function of polymerases, including the polymerase taught by Geneseq AAW29323.

One of ordinary skill in the art would have had an expectation of success to make the claimed mutant polymerases since the methods for mutation of the Y-GG/A regions of known polymerases, such as the one taught by Geneseq AAW29323, were well-known in the art as taught by Truniger et al. and Pissani et al. One of ordinary skill in the art would have further had an expectation of success to make vectors expressing said polymerases and practicing methods of purifying the polymerases and amplifying nucleic acids using the polymerases as taught in the cited references.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Kay Pinkney*, whose telephone number is (703) 305-3553.

SEAN McGARRY
PRIMARY EXAMINER
1635

M. M. Schmidt
June 3, 2002